MOLECULAR BIOLOGY OF
THE CELL
THIRD EDITION

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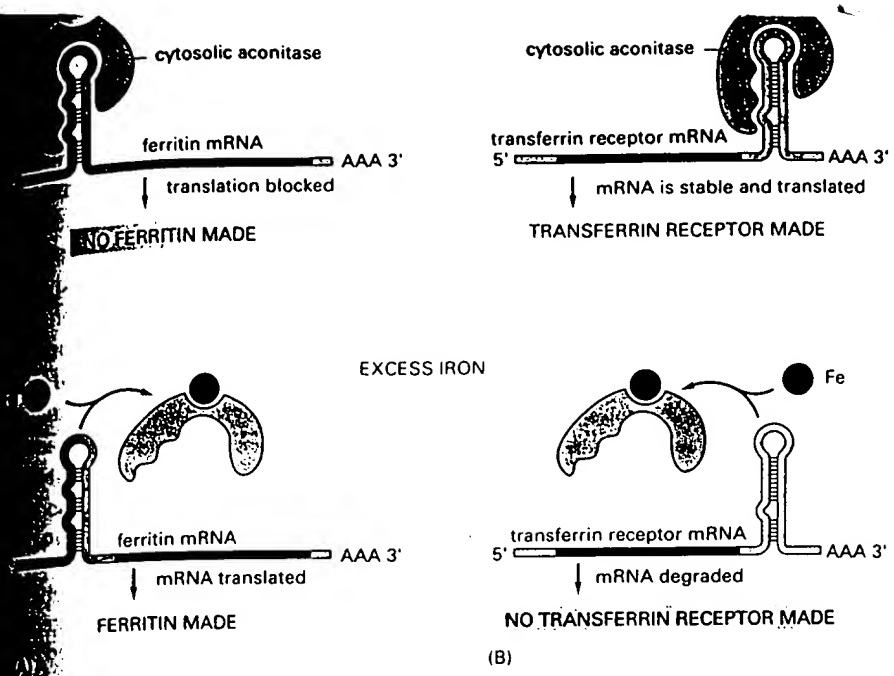

controls mediated by iron. In response to an increase in iron concentration in the cytosol, a cell increases its synthesis of ferritin in order to bind the extra iron (A) and decreases its synthesis of transferrin receptors in order to import less iron (B). Both responses are mediated by the same iron-responsive regulatory protein, aconitase, which recognizes common features in a stem-and-loop structure in the mRNAs encoding ferritin and transferrin receptor. Aconitase dissociates from the mRNA when it binds iron. Because the transferrin receptor and ferritin are regulated by different types of mechanisms, their levels respond oppositely to iron concentrations even though they are regulated by the same iron-responsive regulatory protein. (Adapted from M.W. Hentze et al., *Science* 238:1570–1573, 1987; J.L. Casey et al., *Science* 240:924–928, 1988.)

The stability of an mRNA can be changed in response to extracellular signals. Steroid hormones, for example, affect a cell not only by increasing the transcription of specific genes, but also by increasing the stability of several of the mRNAs encoded by these genes. Conversely, the addition of iron to cells decreases the stability of the mRNA that encodes the receptor protein that binds the iron-transporting protein transferrin, causing less of this receptor to be made. Interestingly, the stability of the transferrin receptor mRNA seems to be modulated by the iron-sensitive RNA-binding protein aconitase, which, as we discussed above, also controls ferritin mRNA translation. Here aconitase binds to the 3′ UTR of the transferrin receptor mRNA and causes an increase in receptor production, presumably by inhibiting the function of sequences that otherwise cause rapid degradation of the mRNA. On the addition of iron, aconitase is released from the mRNA, decreasing mRNA stability (Figure 9–86).

Selective mRNA Degradation Is Coupled to Translation [65]

The control of mRNA stability in eucaryotic cells is best understood for the mRNAs that encode histones. These mRNAs have a half-life of about 1 hour during the DNA synthesis (S) phase of the cell cycle, when new histones are needed, but become unstable and are degraded within minutes when DNA synthesis stops. If DNA synthesis during S phase is inhibited with a drug, histone mRNAs immediately become unstable, perhaps because the accumulation of free histones in the absence of new DNA for them to bind increases the degradation rate of their mRNAs.

The regulation of histone mRNA stability depends on a short 3′ stem-and-loop structure that replaces the poly-A tail present at the 3′ end of other mRNAs (Figure 9–84). A special cleavage reaction, which requires base-pairing to a small RNA in a ribonucleoprotein particle, creates this 3′ end after the histone mRNA is synthesized by RNA polymerase II. If the 3′ end is transferred to other mRNAs by recombinant DNA methods, they also become unstable when DNA synthesis stops. Thus, as for other types of mRNAs, the degradation rate of histone mRNA is strongly influenced by signals near the 3′ end, where mRNA degradation is thought to begin.